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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/697,297	10/27/2000	James M. Robl	P 0277165	3475

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,297	ROBL ET AL.	
	Examiner	Art Unit	
	Joseph Woitach	1632	

-- *The MAILING DATE of this communication appears on th cover she t with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/20/02 (telephone interview)* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *17-32 and 36-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

File

DETAILED ACTION

This application, filed October 27, 2000, claims benefit to provisional application 60/161,987, filed October 28, 1999.

Election/Restriction

Applicant's election without traverse of Group I, claims 1-9, 11-16 and 33-35, in Paper No. 7 is acknowledged. It is noted that Applicants' election indicated that a preliminary amendment would be filed, however no amendment was received. In a telephone interview made August 20, 2002, Examiner contacted Robin Teskin to inquire whether a preliminary amendment had been filed, and was informed that one was not. Applicants indicated that an action on the merits for the application should be made on the pending elected claims.

Claims 1-38 are pending. Upon review of the pending claims it is noted that Groups I and II differ only in claim 10, as it is drawn to use of a haploid male cell. Upon reconsideration, Examiner has decided that it would not be an undue burden to search and exam Group II with elected Group I, therefore, both groups I and II will be examined. Claims 17-32 and 36-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 7. Claims 1-16 and 33-35 are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

The formal drawings were received on July 16, 2001, paper number 4.

Specification

The disclosure is objected to because of the following informalities: The Brief Description of the Drawings contains references to labels which are not present in the figures. Specifically, Figures 1-10 make reference to labeled numbers which are not present in any of the formal drawing submitted.

Appropriate correction is required.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-16 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of using a haploid secondary oocyte with one polar body, does not reasonably provide enablement for use of male germ cells or cells of the blastomere which do not have a polar body. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The instant invention is generally drawn to generating pluripotent embryonic stem cells from the inner cell mass of a blastocyst. More specifically, the method requires that an embryo is generated from metaphase II stage germ cell wherein the polar body is prevented from being extruded resulting in a 2N cell. A review of the art of embryogenesis teaches that only female germ cells, a primary oocyte, contain or result in the extrusion of polar bodies. The specification is silent on how one would affect the presence of a polar body in a male germ cell required to practice the instantly claimed method with any type of male germ cells. Further, the specific methodology taught in the present specification is directed to only manipulating and culturing an oocyte, not male germ cells, and there is no nexus between the methods for activating an oocyte to generate an embryo and the ability to affect this in a male germ cell. Though the process of meiosis in both males and females results in 1N germ cells, the process of meiosis in male and females is fundamentally different. During the process of meiosis in the female three polar

bodies are generated and one functional 1N gamete, however in the male four equal divisions give rise to four 1N gametes. The process and the cells during the process of meiosis are dramatically different between males and females, and the present specification fails to provide any guidance beyond art recognized methods for manipulating primary oocyte to affect the presently claimed method in male germ cells. Additionally, a blastomere is stage in embryogenesis, and neither the male nor the female blastomere has polar bodies.

The specification provides no guidance or teaching on how to affect the presently claimed methods in male germ cells or in blastomere. The specification provides art recognized methods for activating and culturing oocyte however it is silent with respect to methods and guidance for other cell types, and fails to provide any correlation between methods specifically taught and how one would, if possible, adapt the methods for oocyte to any other type of cell from the male, or in blastomere. Without such guidance in the specification and the lack of correlative teaching or working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo*

Nordisk A/S 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is unclear and confusing in the recitation of "a haploid cell in metaphase II that comprises DNA derived form a single individual" because cells undergoing meiosis are only present in an individual. The specification does not set forth methods in which one can generate metaphase II cells by any other means than by isolation of said cell, therefore it is unclear to what other DNA can be present in the cell. The metes and bounds of the claim are unclear because the type of cell encompassed by the claim is not clearly set forth, and appears that it encompasses types of cells not specifically taught in the present specification.

Claims 1 and 16 are unclear in the recitation of "optionally may be genetically modified" and "is genetically modified" because the claims require that the DNA be derived from a single

individual. The claims are confusing because if the DNA contains a heterologous transgene, the DNA would not be from a single individual. Alternatively, if the DNA is from the same individual, it is unclear when the DNA is or was modified. It is unclear if the modification is affected during the instantly claimed method, or prior to obtaining the haploid cells. In this case, the metes and bounds of the claim are not defined because the time the genetic modification is made is not clearly set forth in the claim(s).

Claims 4, 5 and 9 lack antecedent basis for "the haploid DNA". This term is not specifically set forth in preceding claims.

Claim 9 is vague and unclear in the recitation that "the haploid DNA is of a female origin" because it is unclear if both female and male DNA can be obtained from either oocyte or male germ cells, or if the claim is attempting to further limit the type of cell/haploid genome encompassed by the claims to that obtained from a female.

Claim 11 is confusing in the recitation of "containing male or female DNA." First, DNA *per se* is inherently not associated with any sex. Second, the oocyte contains only the X sex chromosome and it is unclear how one would obtain an oocyte with a Y chromosome.

Claim 13-15 are vague and unclear in the recitation of "said cells" because claim 1 makes reference to several types of cells, haploid and diploid. It is unclear to what cells the instant claims refers.

Claim 16 is vague and unclear in the recitation of "is genetically modified" because it is not clear if this is a further method step, or if the haploid cell was obtained from a genetically modified animal, or if a genetic modification is optionally affected during the practice of claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 33 and 34 are rejected under 35U.S.C. 102(a/e) as being anticipated by Thomson (US Patent 5,843,780).

Claims 33 and 34 encompass primate pluripotent embryonic stem cells produced by the method of claim 1. Please note that the cells encompassed by the instant claims are product by

process, and in view of the teaching in the present specification are representative of pluripotent stem cells obtained by other means, in particular those derived from the inner cell mass of a blastocyst. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). Thomson teaches methods of obtaining primate embryonic stem cells from the inner cell mass of a primate. Thomson characterizes the isolated cells and demonstrates that the cells are representative of pluripotent embryonic stem cells. Thus, the cells taught by Thomson anticipates the instantly claimed cells.

Claims 33-35 are rejected under 35U.S.C. 102(e) as being anticipated by Thomson (US Patent 6,200,806).

Claims 33 and 34 are summarized above. Claim 35 encompasses human pluripotent embryonic stem cells produced by the method of claim 1. Please note that the cells encompassed by the instant claims are product by process, and in view of the teaching in the present specification are representative of pluripotent stem cells obtained by other means, in

particular those derived from the inner cell mass of a blastocyst. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). Thomson teaches methods of obtaining human embryonic stem cells from the inner cell mass of a blastocyst. Thomson characterizes the isolated cells and demonstrates that the cells are representative of pluripotent embryonic stem cells. Thus, the cells taught by Thomson anticipates the instantly claimed cells.

Claims 1-9, 11-13 and 33 are rejected under 35U.S.C. 102(b) as being anticipated by Newman-Smith *et al.* (Development, 1995).

The basis of the instant rejection is drawn to the embodiment of using an oocyte in the method set forth in claim 1. Briefly, claim encompasses (a) obtaining a haploid cell in metaphase II, (b) preventing the extrusion of the polar body, (c) culturing the resulting cell into a blastocyst stage, and (d) isolating the inner cell mass cells and culturing said cells. Dependent claims set forth specific cell types (of which oocyte is the object of the rejection), different species of animals, and specific compounds for the prevention of cytokinesis. Newman-Smith *et*

al. teach the isolation of inner cell mass cells from mouse embryos. Specifically, parthenotes were generated by preventing the extrusion of the polar body by cytochalasisn D and then cultured to blastocyst stage of embryogenesis. From the embryos, the inner cell mass cells were isolated and cultured (see materials and methods section, page 2070). Analysis of the resulting cells indicated that some of the cells represented pluripotent stem cells. Newman-Smith *et al.* also teach that similar experiments generating parthenotes indicated that embryos implanted into pseudo-pregnant females gave rise to embryos up to the appearance of limb buds (page 2069, second column).

Though the limitation of implanting the cells is taught by Newman-Smith *et al.*, please note that intended use limitations bear little weight on the determination of patentability. In this case, the limitation "cells that can be used to produce differentiated cells and tissues" does not carry patentable weight in the determination of anticipation for the claimed products. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11-16 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newman-Smith *et al.* (Development, 1995) in further view of Thomson ((US Patent 5,843,780).

The basis of the instant rejection is drawn to the embodiment of using an oocyte in the method set forth in claim 1 wherein the cell is genetically modified. Briefly, claim 1 encompasses (a) obtaining a haploid cell in metaphase II, (b) preventing the extrusion of the polar body, (c) culturing the resulting cell into a blastocyst stage, and (d) isolating the inner cell mass cells and culturing said cells. Claim also includes the limitation wherein the cell may "optionally be genetically modified". Dependent claims set forth specific cell types (of which

oocyte is the object of the rejection), different species of animals, and specific compounds for the prevention of cytokinesis. Dependent claim 16 recites that the cell is genetically modified. As noted above, Newman-Smith *et al.* teach the isolation of inner cell mass cells from mouse embryos. Specifically, parthenotes were generated by preventing the extrusion of the polar body by cytochalasisn D and then cultured to blastocyst stage of embryogenesis. From the embryos, the inner cell mass cells were isolated and cultured (see materials and methods section, page 2070). Analysis of the resulting cells indicated that some of the cells represented pluripotent stem cells. Further, Newman-Smith *et al.* also teach that similar experiments generating parthenotes indicated that embryos implanted into pseudo-pregnant females gave rise to embryos up to the appearance of limb buds (page 2069, second column). However, Newman-Smith *et al.* do not specifically teach to modify the embryonic cells which are generated. Thomson discloses purified preparations of primate and human embryonic stem cells isolated from the ICM of an embryo. Thomson distinguishes the differences in the culturing conditions for the primate embryonic stem cells compared with those for the mouse, however notes that the primate cells can be used for similar experiments and methods previously described for the mouse. Specifically, Thomson proposes genetically modifying the embryonic cells to generate transgenic and knock-out animals (column 1; lines 57-67). In addition, it is proposed to make genetic alterations to the cells to study the affects and mechanisms of differentiation (column 2; lines 1-26). Finally, Thomson proposes that the cells may be used as delivery vehicles for transgenes to provide for the expression of genes for therapeutic benefit in particular disorders (bridging

columns 16 and 17). In summary, at the time of the claimed invention it was proposed that the use of primate and human embryonic stem cells would parallel the use of other embryonic stem cells known in the art. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to use the cells generated by Newman-Smith *et al.* in methods which were readily known in the art for other embryonic stem cells. As specifically suggested by Thomson, one of ordinary skill in the art would have been motivated to genetically modify a embryonic stem cell for a variety of reasons, including the generation of transgenic animals, the study of differentiation, and as delivery vehicles. Given the successful use of other embryonic stem cells known in the art, there would have been a reasonable expectation of success to adapt the methodology for one type of embryonic stem cell, to cells isolated by other means or methods.

Thus, the claimed invention, as a whole was *prima facie* obvious absent to the evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

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